Remarks

The Office Action mailed 17 December 2002 has been received and reviewed. Claim 22 having been cancelled, claims 1, 13-15, 23, 25, and 30 having been amended, and claims 34-38 having been added, the pending claims are claims 1-21 and 23-38. Reconsideration and withdrawal of the rejections are respectfully requested.

The new and amended claims are fully supported by the specification and originally filed claims. For example, the amendments to claims 1, 23, and 30 are supported by the originally filed claims, e.g., claim 22. New claim 34 is supported by the specification at page 5, lines 7-28. New claims 35-38 are supported by originally filed claims 1, 2, 4, 6, 22, 23, and 30, for example. No new matter has been added.

The 35 U.S.C. §112, Second Paragraph, Rejection

The Examiner rejected claims 13-15 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner alleged that claims 13-15 recite the limitation "the skin permeation enhancer" in line one of each claim with insufficient antecedent basis for this limitation. The Examiner further alleged that the delivery enhancing adjuvant to Claim 10 is also known as a skin permeation enhancer.

This rejection is traversed and clarified by the addition of claim 34, which states that the delivery enhancing adjuvant is a skin permeation enhancer, and the amendments of claims 13-15. These amended and new claims clarify that the delivery enhancing adjuvant can be a skin permeation enhancer, as described in the specification at page 5, lines 7-28. These terms are not necessarily used synonymously.

The 35 U.S.C. §103 Rejection

The Examiner rejected claims 1-33 under 35 U.S.C. §103(a) as being unpatentable over Garbe et al. (WO 96/08229) in view of Cleary (EP 0483105 A1). This rejection is respectfully traversed.

Although the Examiner is correct in his interpretation of WO 96/08229 (Garbe), there is no specific teaching or suggestion of a composition that includes about 8% to about 30% fentanyl. Fentanyl is listed as one of many drugs that can be included in the composition of Garbe in an amount of about 0.01 to about 30 percent by weight. The claims of the present invention recite a subset of the Garbe range -- about 8% to about 30% -- wherein the compositions are substantially free of undissolved fentanyl.

Show the criticality

Fentanyl is known to be rather difficult to solubilize in acrylate compositions. In fact, it is Applicants' Representatives understanding that it is known to be very difficult to incorporate fentanyl in a drug delivery composition, particularly an acrylate composition, in an amount over 5 percent by weight. See Exhibit A, page 492, column 2. The amount of fentanyl soluble in various pressure sensitive adhesives is listed in Table 1. These numbers are in milligrams per milliliter. Assuming that the density of each of the adhesives is 1.0 gram per milliliter, the fentanyl is soluble in an acrylate adhesive in an amount of only 2.19 percent by weight (21.9 mg/mL ÷ 1.0 g/mL x 1 g/1000 mg x 100 = 2.19 wt-%).

Applicants were able to develop compositions that include fentanyl in an amount of about 8% to about 30% with substantially no undissolved fentanyl. Such an amount can provide a device that can deliver fentanyl over a relatively long period of time (e.g., about 0.5 to about 5.0 mg/day thereby causing the serum concentration of fentanyl in a mammal to be about 0.2 to about 10 ng/mL for a period of time from about 4 to about 14 days, as recited in claims 30). There is no specific teaching or suggestion in Garbe of the combination of components capable of providing this range of fentanyl, nor this specific level of delivery.

Limitations in the claims? criticality?

Furthermore, with respect to independent claim 23, although Garbe does teach the recited delivery enhancing adjuvants, there is no specific teaching that they can be used in combination

with fentanyl for any significant advantage. Thus, although Garbe teaches the use of fentanyl, methyl laurate, and tetraglycol, there is no specific teaching or suggestion of this combination in a composition that includes about 8% to about 30% fentanyl with substantially no undissolved fentanyl.

Thus, it is respectfully submitted that it is not routine experimentation to develop a composition that includes 8% to 30% fentanyl with substantially no undissolved fentanyl in the composition. Furthermore, Cleary does not add that which is missing from Garbe. There is no teaching or suggestion of a relatively high level of fentanyl in a drug delivery composition with substantially no undissolved fentanyl.

Summary

It is respectfully submitted that the pending claims 1-21 and 23-38 are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted for
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CERTIFICATE UNDER 37 CFR §1.8:
The undersigned hereby certifies that this paper is being transmitted by facsimile in accordance with 37 CFR §1.6(d) to the Patent and Trademark Office, addressed to Assistant Commissioner for Patents, Washington, D.C. 20231, on this 17th day of March, 2003, at 7pm (Central Time).

By: Ann M. Mueting
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APPENDIX A - SPECIFICATION/CLAIM AMENDMENTS
INCLUDING NOTATIONS TO INDICATE CHANGES MADE
Serial No.: 09/965,610
Docket No.: 56032US002

Amendments to the following are indicated by underlining what has been added and bracketing what has been deleted.

In the Claims

For convenience, all pending claims are shown below.

1. (AMENDED) A transdermal drug delivery composition comprising:

(a) a copolymer comprising:

(i) one or more A monomers selected from the group consisting of alkyl acrylates containing 4 to 12 carbon atoms in the alky group and alkyl methacrylates containing 4 to 12 carbon atoms in the alkyl group; and

(ii) one or more ethylenically unsaturated B monomers copolymerizable with the A monomer; and

(b) about 8% to about 30% by weight fentanyl based on the total weight of the composition;

wherein the composition is substantially free of undissolved fentanyl.

2. The composition of claim 1 wherein the A monomer is selected from the group consisting of isooctyl acrylate, 2-ethylhexyl acrylate, butyl acrylate, and cyclohexyl acrylate.

3. The composition of claim 1 wherein the A monomer is isooctyl acrylate.

4. The composition of claim 1 wherein the B monomer is selected from the group consisting of 2-hydroxyethyl acrylate, 2-hydroxyethyl methacrylate, glyceryl acrylate, N, N-diethylacrylamide, 2-ethoxyethoxyethyl acrylate, 2-ethoxyethyl acrylate, tetrahydrofurfuryl acrylate, acrylic acid, acrylamide, vinyl acetate, N-vinyl pyrrolidone and mixtures thereof.

5. The composition of claim 1 wherein the B monomer is 2-hydroxyethyl acrylate.

6. The composition of claim 5 wherein the copolymer comprises from about 5% to about 45% of 2-hydroxyethyl acrylate by weight based on the total weight of all monomers in the copolymer.

7. The composition of claim 1 wherein the copolymer further comprises a macromonomer.

8. The composition of claim 7 wherein the macromonomer is a functionally terminated polymethylmethacrylate.

9. The composition of claim 7 wherein the copolymer contain from about 1% to about 6% of macromonomer by weight based on the total weight of all monomers in the copolymer.

10. The composition of claim 1 wherein the composition further comprises a delivery enhancing adjuvant.

11. The composition of claim 10 wherein the delivery enhancing adjuvant is selected from the group consisting of alkane polyols, fatty acids, fatty acid esters, fatty alcohols, terpenes, C_5-C_{18} alkyl esters of a caraboxylic acid, and mixtures thereof.

12. The composition of claim 10 wherein the delivery enhancing adjuvant is selected from the group consisting of ethyl oleate, isopropyl myristate, glycerol, tetraglycol, methyl laurate, N,N-dimethyldodecylamine N-oxide, limonene, terpineol, tetraethylene glycol, menthol, and mixtures thereof.

13. (AMENDED) The compositions of claim 10 wherein the concentration of [skin permeation enhancer] the delivery enhancing adjuvant is from about 5% to about 40% by weight based on the total weight of the composition.

14. (AMENDED) The composition of claim [10] 34 wherein the skin permeation enhancer is tetraglycol.

15. (AMENDED) The composition of claim [10] 34 wherein the skin permeation enhancer is methyl laurate.

16. The composition of claim 1 wherein the concentration of fentanyl in said transdermal drug delivery composition is from about 12% to about 24% by weight.

17. The composition of claim 7 wherein the copolymer comprises from about 50 to about 94% isooctyl acrylate, about 5% to about 40% 2-hydroxyethyl acrylate, about 1% to about 6% macromonomer, and 0% to about 20% vinyl acetate by weight.

18. The composition of claim 7 wherein the copolymer comprises from about 52% to about 60% isooctyl acrylate, about 35% to about 40% 2-hydroxyethyl acrylate, about 1% to about 4% macromonomer, and 0% to about 10% vinyl acetate by weight.

19. The composition of claim 17 wherein the concentration of fentanyl is from about 12% to about 22% by weight, wherein the composition further comprises about 15% to about 35% by weight of a permeation enhancer selected from the group consisting of methyl laurate, tetraglycol, and mixtures thereof.

20. The composition of claim 19 wherein the concentration of fentanyl is from about 12% to

about 17% by weight and the concentration of methyl laurate is from about 20% to about 35% by weight.

21. The composition of claim 19 wherein the concentration of fentanyl is from about 15% to about 22% by weight and the concentration of tetraglycol is from about 15% to about 25% by weight.

22. (CANCELLED)

23. (AMENDED) [The] A pressure sensitive adhesive composition for the transdermal delivery of fentanyl comprising:

(a) an acrylate polymer;

(b) about 8% to about 30% by weight fentanyl based on the total weight of the composition; and

(c) a delivery enhancing adjuvant selected from the group consisting of methyl laurate, tetraglycol, and mixtures thereof;

wherein the composition is substantially free of undissolved fentanyl.

24. The composition of claim 23 wherein the concentration of delivery enhancing adjuvant is from about 5% to about 40% by weight based on the total weight of the composition.

25. (AMENDED) The composition of claim 23 wherein the [pressure sensitive adhesive copolymer comprises a copolymer comprising] acrylate polymer comprises:

(a) one or more A monomers selected from the group consisting of alkyl acrylates containing 4 to 12 carbon atoms in the alkyl group and alkyl methacrylates containing 4 to 12 carbon atoms in the alkyl group; and

(b) one or more ethylenically unsaturated B monomers copolymerizable with the A

monomers.

26. The composition of claim 25 wherein the B monomer is selected from the group consisting of 2-hydroxyethyl acrylate, 2-hydroxyethyl methacrylate, glycerol acrylate, N,N-diethylacrylamide, 2-ethoxyethoxyethyl acrylate, 2-ethoxyethyl acrylate, tetrahydrofurfuryl acrylate, N-vinyl prrolidone and mixtures thereof.

27. A device for the transdermal delivery of fentanyl comprising a backing and a composition according to claim 1, said composition being adhered to one surface of the backing.

28. A method of treating in a mammal a condition capable of treatment by fentanyl comprising the steps of:

(a) providing a composition according to claim 1;

(b) placing the composition on the skin of a mammal; and

(c) allowing the composition to remain on the skin for a time sufficient to establish or maintain a therapeutically effective blood level of fentanyl in the mammal.

29. A method of providing analgesia to a mammal comprising the steps of:

(a) providing a composition according to claim 1;

(b) placing the composition on the skin of a mammal; and

(c) allowing the composition to remain on the skin for a time sufficient to establish or maintain an analgesically effective blood level of fentanyl in the mammal.

30. (AMENDED) A method of providing sustained analgesia to a mammal comprising delivering fentanyl to a mammal via a transdermal drug delivery device in an amount of about

0.5 to about 5.0 mg/day thereby causing the serum concentration of fentanyl in the mammal to be about 0.2 to about 10 ng/mL for a period of time from about 4 to about 14 days, wherein the device includes a composition comprising an acrylate polymer and about 8% to about 30% by weight fentanyl based on the total weight of the composition, wherein the composition is substantially free of undissolved fentanyl.

31. The method of claim 30 wherein the fentanyl is delivered in an amount of 0.5 to about 2.5 mg/day, the serum concentration of fentanyl in the mammal is about 0.3 to about 4 ng/mL, and the period of time is from about 6 to about 8 days.

32. A device for the transdermal delivery of fentanyl comprising:

(a) a drug reservoir layer comprising the composition of claim 1;

(b) a rate controlling membrane adhered to one surface of the drug reservoir layer; and

(c) a skin contacting pressure sensitive adhesive layer adhered to the surface of the membrane that is opposed to the surface of the membrane in contact with the reservoir layer.

33. A device for the transdermal delivery of fentanyl comprising:

(a) a drug reservoir layer comprising the composition of claim 17;

(b) a rate controlling membrane adhered to one surface of the drug reservoir layer; and

(c) a skin contacting pressure sensitive adhesive layer adhered to the surface of the membrane that is opposed to the surface of the membrane in contact with the reservoir layer.

34. (NEW) The composition of claim 10 wherein the delivery enhancing adjuvant is a skin

permeation enhancer.

35. (NEW) A transdermal drug delivery composition comprising:

(a) a copolymer comprising:

(i) one or more A monomers selected from the group consisting of isooctyl acrylate, 2-ethylhexyl acrylate, butyl acrylate, and cyclohexyl acrylate; and

(ii) one or more ethylenically unsaturated B monomers copolymerizable with the A monomer; wherein the B monomers are selected from the group consisting of 2-hydroxyethyl acrylate, 2-hydroxyethyl methacrylate, glyceryl acrylate, N, N-diethylacrylamide, 2-ethoxyethoxyethyl acrylate, 2-ethoxyethyl acrylate, tetrahydrofurfuryl acrylate, acrylic acid, acrylamide, vinyl acetate, N-vinyl pyrrolidone and mixtures thereof; and

(b) about 8% to about 30% by weight fentanyl based on the total weight of the composition;

wherein the composition is substantially free of undissolved fentanyl.

36. (NEW) A transdermal drug delivery composition comprising:

(a) a copolymer comprising:

(i) one or more A monomers selected from the group consisting of isooctyl acrylate, 2-ethylhexyl acrylate, butyl acrylate, and cyclohexyl acrylate; and

(ii) about 5% to about 45% of one or more ethylenically unsaturated B monomers copolymerizable with the A monomer; wherein the B monomers are selected from the group consisting of 2-hydroxyethyl acrylate, 2-hydroxyethyl methacrylate, glyceryl acrylate, N, N-diethylacrylamide, 2-ethoxyethoxyethyl acrylate, 2-ethoxyethyl acrylate, tetrahydrofurfuryl acrylate, acrylic acid, acrylamide, vinyl acetate, N-vinyl pyrrolidone and mixtures thereof; and

(b) about 8% to about 30% by weight fentanyl based on the total weight of the composition;

wherein the composition is substantially free of undissolved fentanyl.

37. (NEW) A transdermal drug delivery device comprising a composition comprising:

(a) a copolymer comprising:

(i) one or more A monomers selected from the group consisting of alkyl acrylates containing 4 to 12 carbon atoms in the alky group and alkyl methacrylates containing 4 to 12 carbon atoms in the alkyl group; and

(ii) one or more ethylenically unsaturated B monomers copolymerizable with the A monomer; and

(b) about 8% to about 30% by weight fentanyl based on the total weight of the composition;

wherein the composition is substantially free of undissolved fentanyl; and

wherein the drug delivery device delivers fentanyl to a mammal in an amount of about 0.5 to about 5.0 mg/day thereby causing the serum concentration of fentanyl in the mammal to be about 0.2 to about 10 ng/mL for a period of time from about 4 to about 14 days.

38. (NEW) A transdermal drug delivery composition comprising:

(a) a copolymer comprising:

(i) one or more A monomers selected from the group consisting of isooctyl acrylate, 2-ethylhexyl acrylate, butyl acrylate, and cyclohexyl acrylate; and

(ii) about 5% to about 45% of one or more ethylenically unsaturated B monomers copolymerizable with the A monomer; wherein the B monomers are selected from the group consisting of 2-hydroxyethyl acrylate, 2-hydroxyethyl methacrylate, glyceryl acrylate, N, N-diethylacrylamide, 2-ethoxyethoxyethyl acrylate, 2-ethoxyethyl acrylate,

tetrahydrofurfuryl acrylate, acrylic acid, acrylamide, vinyl acetate, N-vinyl pyrrolidone and mixtures thereof;

(b) about 8% to about 30% by weight fentanyl based on the total weight of the composition; and

(c) a delivery enhancing adjuvant selected from the group consisting of methyl laurate, tetraglycol, and mixtures thereof;

wherein the composition is substantially free of undissolved fentanyl.